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ORIGINAL RESEARCH

A Streamlined Diagnostic Process Improved the Outcomes of Patients with Adult-Onset Still's Disease: A Single-Center Retrospective Observational Study

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ABSTRACT

Introduction: The diagnosis of adult-onset Still's disease (AOSD) is often delayed due to its clinical heterogeneity and lack of pathognomic features. Hence, there is an unmet need for an efficient diagnostic process. The major aim of this study was to compare the differences in disease outcomes between two groups of AOSD patients with and without implementation of the streamlined diagnostic process (SDP).

Methods: Of 172 febrile patients with skin rash and/or arthralgia, 112 individuals had AOSD. The tentative diagnosis of AOSD or non-AOSD was made with or without the SDP implementation. The selection criteria for AOSD outcomes analysis were as follows: (1) age at study entry older than 20 years, (2) fulfillment of the Yamaguchi criteria for AOSD diagnosis, and (3) a follow-up period longer than 6 months after initiation of therapy. Three outcome parameters were evaluated, including diagnosis lag period, the proportion of "early diagnosis," and the

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proportion of achieving disease remission after a 6-month therapy.

Results: The SDP was implemented for expediting AOSD diagnosis in 41 (36%) enrolled patients (SDP-implemented group). The diagnosis lag period was significantly shorter in the SDP-implemented group (median 2.0 weeks, interquartile range [IQR] 1.0–2.5 weeks) than in the non-SDP-implemented group (4.0 weeks, IQR 2.0–6.0 weeks, $p < 0.001$). A significantly higher proportion of "early diagnosis" was also found in the SDP-implemented group (75.6%) compared with the non-SDP-implemented group (33.8%, $p < 0.001$). We revealed a significantly higher proportion of achieving remission in the SDP-implemented group (85.4%) compared with the non-SDP-implemented group (67.6%, $p < 0.05$). Logistic regression analysis revealed SDP implementation as a potential predictor of achieving disease remission.

Conclusions: Implementing an SDP for expediting diagnosis could improve outcomes for AOSD patients. This diagnostic process increased the early diagnosis rate and led to a higher disease remission rate. However, the beneficial effects of SDP implementation need further external validation.

Keywords: Streamlined diagnostic process (SDP); Lag period; Disease remission; Outcomes; Adult-onset Still's disease

Key Summary Points

Why carry out this study?
The diagnosis of adult-onset Still's disease (AOSD) is usually delayed.
A streamlined diagnostic process (SDP) would reduce unnecessary evaluation or intervention, especially invasive procedures or ineffective antibiotics treatment.
What was learned from the study?
The SDP, which mainly detects the presence of neutrophilia, hyperferritinemia, and a high interleukin (IL)-18 level, is proposed to expedite AOSD diagnosis.
Implementing the SDP may increase the probability of an early diagnosis of AOSD
A significantly higher proportion of patients in the SDP-implemented group achieved disease remission than in the non-SDP-implemented group.

INTRODUCTION

Adult-onset Still's disease (AOSD) is a multisystemic autoinflammatory disorder characterized by fever, evanescent rash, arthralgia or arthritis, sore throat, liver dysfunction, increased acute phase reactants, and hyperferritinemia. It is sometimes associated with life-threatening complications such as macrophage activation syndrome (MAS) and pulmonary involvement [1–5]. Although uncommon, AOSD has been increasingly recognized as an important cause of fever of unknown origin (FUO) [6] and one of the most common rheumatological causes of FUO [7]. In the absence of pathognomic clinical features or pathological findings, the diagnosis of AOSD Is made by excluding infectious diseases, malignancies, and other rheumatic diseases [8]. Its diagnosis is often delayed in the early stage, which impedes optimal therapy for patients. Therefore, there is an unmet need to utilize the available diagnostic biomarkers to diagnose AOSD efficiently.

Hyperferritinemia, a significant feature of several autoinflammatory diseases, has long been considered a disease marker and an activity indicator of AOSD [9–11]. Fautrel et al. proposed a five-fold increase of serum ferritin levels as a specific marker for diagnosing AOSD [12]. Lian et al. observed that combined Yamaguchi

criteria and hyperferritinemia gave a better prediction of AOSD [13]. Kim et al. also proposed a combinational score of systemic immune-inflammation index and ferritin as a useful tool for diagnosing AOSD [14]. Recently, a clinician-friendly algorithm including neutrophilia and hyperferritinemia was built to discriminate AOSD from other causes of FUO [15]. Based on these observations, we proposed a streamlined diagnostic process (SDP) (Fig. 1) with enrollment of both hyperferritinemia and neutrophilia as the first-line markers for expediting AOSD diagnosis.

Increased proinflammatory cytokines, including interleukin (IL)-1β, IL-6, IL-18, and tumor necrosis factor (TNF)-α, also play a pathogenic role in AOSD [10, 16–18], and the most crucial cytokine is probably IL-18. Kudela et al. reported a high specificity in using elevated IL-18 levels for AOSD diagnosis [19]. The results of previous studies showed that increased IL-18 levels could discriminate AOSD from other rheumatic diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's syndrome [20, 21]. Besides, Priori et al. demonstrated that IL-18 levels above a cutoff of 148.9 pg/ml could discriminate active AOSD from sepsis [22], and Zhang et al. proposed that plasma IL-18 and ferritin levels could be used to differentiate bloodstream infection (BSI) from AOSD [23]. Among the inflammatory diseases presented with a cytokine storm and hyperferritinemia [24], active AOSD patients had higher IL-18

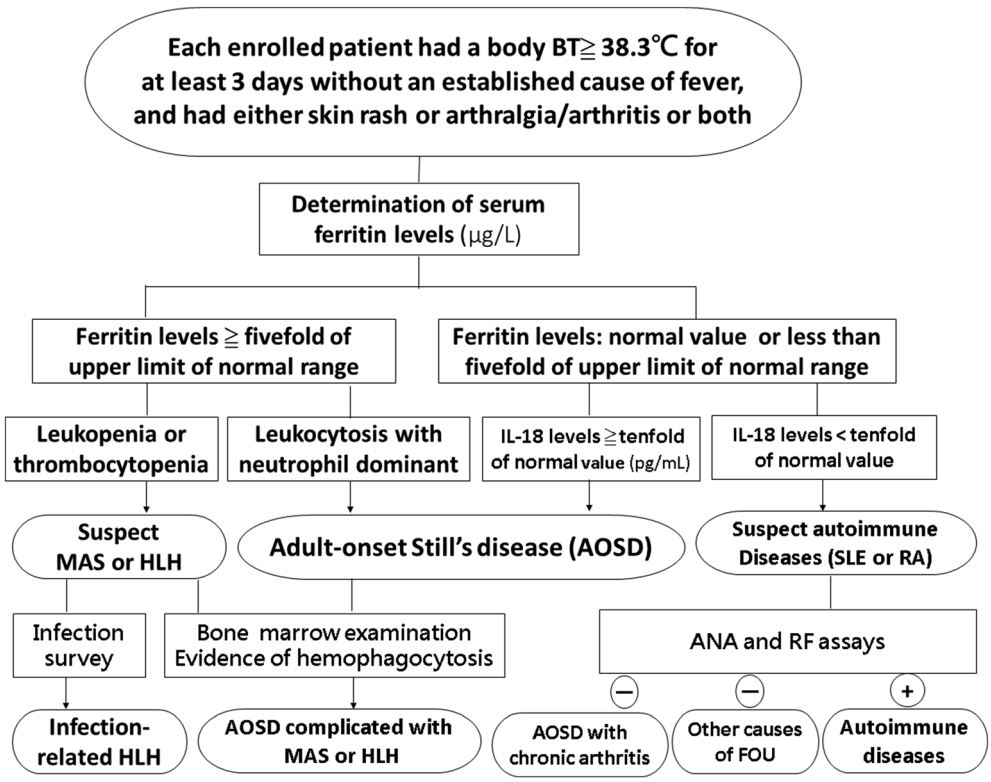

Fig. 1 The proposed streamlined diagnostic process (SDP) for diagnosing adult-onset Still's disease (AOSD). leukocytosis as leukocyte counts ≧11,000/mm^3; neutrophil dominance if neutrophil proportion more than 75% of total leukocyte counts; leukopenia as leukocyte counts less than 4000/mm^3; thrombocytopenia as platelet counts less than 50,000/mm^3, *IL-18* interleukin-18, *MAS* macrophage activation syndrome, *HLH* hemophagocytic lymphohistiocytosis, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *ANA* antinuclear antibodies, *RF* rheumatoid factor, *FUO* fever of unknown origin. The upper limit of serum ferritin level was 306.8 μg/l; the normal value of serum IL-18 level was less than 12.3 pg/ml

levels than severe coronavirus disease 2019 (COVID-19) patients [25, 26] and IL-18 was a potential discriminator between active AOSD and severe COVID-19 [26]. These findings suggest IL-18 as the diagnostic biomarker of AOSD [27]. Hence, we integrated a high IL-18 level, the second-line marker, into the SDP for expediting diagnostic process of AOSD in febrile patients without sufficient hyperferritinemia (Fig. 1). We adopted a ten-fold normal value of IL-18 as the discriminative cut-off point (123.0 pg/ml) since it is close to the lowest cut-off value (148.9 pg/ml) of IL-18 levels in AOSD patients proposed by Priori et al. [22]. Given the similarities in clinical manifestations between AOSD and infection, malignancy, or other autoimmune diseases, the diagnosis of AOSD was made by exclusion of these diseases. We speculated that an implementation of SDP may expedite the diagnostic process of AOSD. The major aim of this retrospective study was to compare the differences in disease outcomes between two groups of AOSD patients with and without SDP implementation.

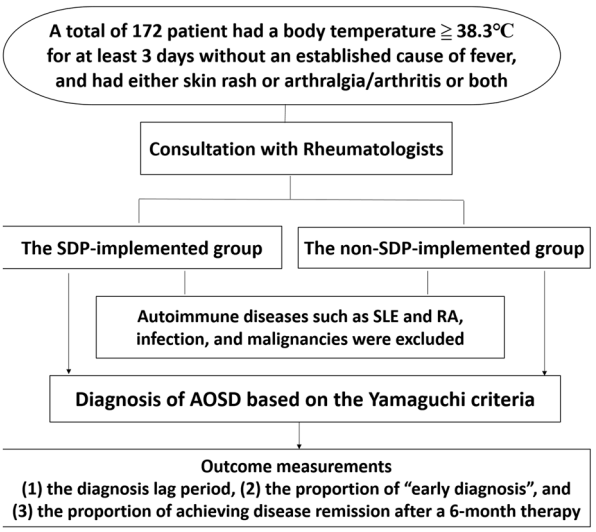

Fig. 2 Study design workflow in the present retrospective study. *AOSD* adult-onset Still's disease, *SDP* streamlined diagnostic process, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis

METHODS

Patients and Study Design

This retrospective, single-center, observational study was conducted at China Medical University Hospital (CMUH) between March 2017 and January 2022. The study design was illustrated in Fig. 2. A total of 172 patients who presented with a fever above 38.3 °C for at least 3 days without an established cause, skin rash, or/and arthralgia/arthritis were referred to the rheumatologists in CMUH. Although the SDP may expedite the diagnostic process of AOSD, the decision to implement SDP before using the Yamaguchi criteria for final diagnosis of AOSD was based on the judgment of each attending physician. The selection criteria for AOSD disease outcomes analysis were as follows: (1) age at study entry older than 20 years, (2) fulfillment of the Yamaguchi criteria for diagnosis of AOSD [8], and (3) a follow-up period longer than 6 months after initiation of therapy. Besides, patients with infection, malignancies, or autoimmune diseases such as SLE or RA were excluded from the final analysis. The systemic activity was assessed using a modified Pouchot score as described by Rau et al. [28]. This systemic activity score (range 0–12) assigns one point to each of 12 manifestations: fever, evanescent rash, sore throat, arthralgia or arthritis, myalgia, pleuritis, pericarditis, pneumonitis, lymphadenopathy, hepatomegaly or abnormal liver function, elevated leukocyte count $\geqq 15{,}000/mm^3$, and serum ferritin levels > 3000 μg/L.

Patients' data were reviewed, including demographics, medical history, the results of clinical and laboratory assessments, the use of concomitant corticosteroids, the conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), and the biologic DMARDs used were reviewed. Baseline IL-18 levels were determined only in the SDP-implemented group of patients. The Institutional Review Board of the hospital approved this study (CMUH110-REC2-106), and the written consent was waived because this is a retrospective analysis.

Determination of Inflammatory Parameters

Erythrocyte sedimentation rate (ESR) was determined using the Westergren method (Sed Rate Screener 20/II, Greiner bio-one, Austria). Serum ferritin levels were determined by a chemiluminescent immunoassay sandwich method (two-site immunoenzymatic assay, Beckman Coulter, Inc., Brea, CA, USA), and C-reactive protein (CRP) levels by an immunoturbidimetric method (Beckman Coulter, Inc., Brea, CA, USA). Serum IL-18 levels were determined by the enzyme-linked immunosorbent assay (ELISA) kits (Medical & Biology Laboratories Co, Ltd., Naka-Ku, Nagoya, Japan) according to the manufacturer's instructions.

Outcome Measurements

There is no generally accepted definition of disease remission in AOSD. In the present study, the therapeutic response after a 6-month therapy was categorized into (1) complete remission if all the baseline clinical manifestations and laboratory abnormalities had resolved, (2) partial remission if only one baseline clinical manifestation or laboratory abnormality persisted, or (3) poor response if two or more baseline clinical manifestations or laboratory abnormalities persisted at the time of assessment [26]. We defined disease remission as patients with complete or partial remission.

A total of three outcome measurements, including the diagnosis lag period, the proportion of "early diagnosis", and the proportion of achieving disease remission after a 6-month therapy, were evaluated in the enrolled AOSD patients. The diagnosis lag period was defined as the interval between the date of the first symptoms and the date of established diagnosis. Early diagnosis of AOSD was defined as a diagnosis lag period not longer than 2 weeks.

Statistical Analysis

The results were presented as the mean ± standard deviation (SD) or median (interquartile range). We performed a chi-squared test to examine the between-group difference of categorical variables. The independent Student's *t* test was used for the between-group comparison of numerical variables. We also constructed both univariate and multivariable logistic regression models to identify factors predictive of disease remission assessed at week 24 of treatment. The missing values were excluded from the statistical analysis. A two-sided probability of less than 0.05 was considered significant.

RESULTS

Clinical Characteristics of AOSD Patients

Of 172 participants, 112 individuals had AOSD (Table 1). Among the enrolled 112 AOSD patients, spiking fever (≥ 39 °C), rash, arthralgia or arthritis, sore throat, liver dysfunction, and lymphadenopathy were noted in 112 (100%), 92 (82.1%), 86 (76.8%), 51 (45.5%), 41 (36.6%), and 18 (16.1%) patients, respectively. The SDP was implemented for the diagnosis of AOSD (SDP-implicated group) in 41 (36%) of the enrolled participants. As illustrated in Table 1, the patients of the SDP-implemented group were significantly older than the non-SDP-implemented group patients. However, there was no significant difference in the female proportion, clinical manifestations, baseline systemic activity scores, baseline activity parameters, or medication use after AOSD diagnosis between the SDP-implemented and non-SDP-implemented groups (Table 1). As illustrated in Fig. 3, five patterns of diagnostic results depending on the combination of SDP implementation and the Yamaguchi criteria of AOSD. Four febrile patients with skin rash and/or arthritis were discordant based on initial SDP implementation and the Yamaguchi criteria for final diagnosis. Two febrile patients who presented with skin rash, arthritis, hyperferritinemia, and neutrophilia leukocytosis had the high likelihood of AOSD diagnosis using the SDP, while the diagnosis of dermatomyositis with interstitial lung disease was finally made. The other two patients who manifested with fever, palpable cervical lymph nodes, hyperferritinemia, and

Table 1 Demographic data and baseline characteristics of adult-onset Still's disease (AOSD) patients with and without a streamlined diagnostic process (SDP)[a]

Characteristics at baseline	SDP-implicated group (n = 41)	Non-SDP-implicated group (n = 71)
Age at study entry, years	48.2 ± 13.7*	43.0 ± 15.7
Female proportion, n (%)	30 (73.2%)	53 (74.6%)
Fever, n (%)	41 (100.0%)	71 (100.0%)
Evanescent rash, n (%)	36 (87.8%)	56 (78.9%)
Arthralgia or arthritis, n (%)	29 (70.7%)	57 (80.3%)
Sore throat, n (%)	20 (48.8%)	31 (43.7%)
Lymphadenopathy, n (%)	8 (19.5%)	10 (14.1%)
Liver dysfunction, n (%)	17 (41.5%)	24 (33.8%)
ESR, mm/1st hour	32.7 ± 27.4	38.5 ± 30.6
CRP, mg/dl	3.11 ± 4.36	4.61 ± 6.91
Ferritin levels, μg/l	1040 ± 1022	1460 ± 2057
Systemic activity scores	4.59 ± 1.22	4.42 ± 1.20
WBC, count/mm^3	12,860 ± 5430	13,000 ± 6950
Neutrophil percentage	75.2 ± 11.1	77.0 ± 12.7
Lymphocyte percentage	20.2 ± 10.2	17.8 ± 15.7
Neutrophil/lymphocyte ratio	5.62 ± 4.64	8.55 ± 11.3
Hemoglobin, g/dl	13.5 ± 1.4	12.9 ± 1.8
Platelet, × 1000/mm^3	310.8 ± 120.2	322.1 ± 123.5
Diagnostic lag period, weeks	2.0 (1.0–2.5)**	4.0 (2.0–6.0)
Used medications after Dx		
Corticosteroids, n (%)	38 (92.7%)	66 (93.0%)
The used dose of corticosteroids, mg/day	30.0 ± 16.3	36.6 ± 19.2
Methotrexate, n (%)	28 (68.3%)	43 (60.6%)
Hydroxychloroquine, n (%)	35 (85.4%)	50 (70.4%)
Cyclosporine, n (%)	9 (22.0%)	22 (31.0%)
Azathioprine, n (%)	6 (14.6%)	8 (11.3%)
Tocilizumab, n (%)	4 (9.8%)	8 (11.3%)
Follow-up period, years	3.17 ± 1.05	2.74 ± 1.27
Outcome measurements		
Proportion of "early Dx.", n (%)	31 (75.6%)**	24 (33.8%)

Table 1 continued

Characteristics at baseline	SDP-implicated group (n = 41)	Non-SDP-implicated group (n = 71)
Remission rate after 6 months Rx., n (%)	35 (85.4%)*	48 (67.6%)

NA not applicable, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *Dx.* diagnosis, *Rx* treatment, *WBC* white blood cells

Liver dysfunction was defined as serum levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≧ 40 IU/l

[a]Data presented as mean ± SD, median (25th–75th quartile range) or number (%)

*$p < 0.05$, vs. non-SDP-implicated group, as determined by chi-square test

*$p < 0.05$

**$p < 0.001$, vs. non-SDP-implicated group, as determined by Mann–Whitney U test

elevated erythrocyte sedimentation rate were suspected to be AOSD using the SDP, while a final diagnosis of B cell lymphoma was made (Fig. 4).

Comparison of the Outcome Measurements Between the SDP-Implemented Group and Non-SDP-Implemented Group

As shown in Table 1, the diagnosis lag period was significantly shorter in the SDP-implemented group (median 2.0 weeks, interquartile range [IQR] 1.0–2.5 weeks) than in the non-SDP-implemented group (4.0 weeks, IQR 2.0–6.0 weeks, $p < 0.001$). As shown in Fig. 3, there was a significantly higher proportion of "early diagnosis" in the SDP-implemented group (75.6%) compared with the non-SDP-implemented group (33.8%, $p < 0.001$). A significantly higher proportion of patients achieving disease remission was also observed in the SDP-implemented group (85.4%) compared with the non-SDP-implemented group (67.6%, $p < 0.05$).

Logistic Regression Analyses for Predicting Disease Remission After 6 Months of Therapy

We used logistic regression analysis to identify the potential factors capable of predicting partial or complete remission after a 6-month therapy. As illustrated in Table 2, the univariate regression analysis identified that SDP implementation, the presence of evanescent rash, baseline CRP levels, and baseline hemoglobin levels were significant predictors of disease remission. The multivariate regression analysis also identified evanescent rash and baseline CRP levels as significant predictors of disease remission. Although there was no statistical significance in multivariate analysis, SDP implementation was a potential positive predictor for achieving disease remission after a 6-month therapy in AOSD patients.

DISCUSSION

Early diagnosis of AOSD is often a challenge due to its heterogeneous clinical manifestations and lack of pathognomic features [1–3, 29]. Herein, we evaluated the impact of SDP implementation on the outcomes of AOSD patients and whether it would expedite the diagnostic process of AOSD. Our results showed better outcomes for the SDP-implemented group of patients, including a higher probability of "early diagnosis" and a higher proportion of achieving disease remission. Moreover, our logistic regression analysis revealed SDP implementation as a potential predictor of achieving disease remission after a 6-month therapy. These observations indicate that SDP implementation could improve the outcomes of AOSD patients.

The ambiguity in clinical features and the absence of characteristic biomarkers for diagnosis hamper an early diagnosis of AOSD in

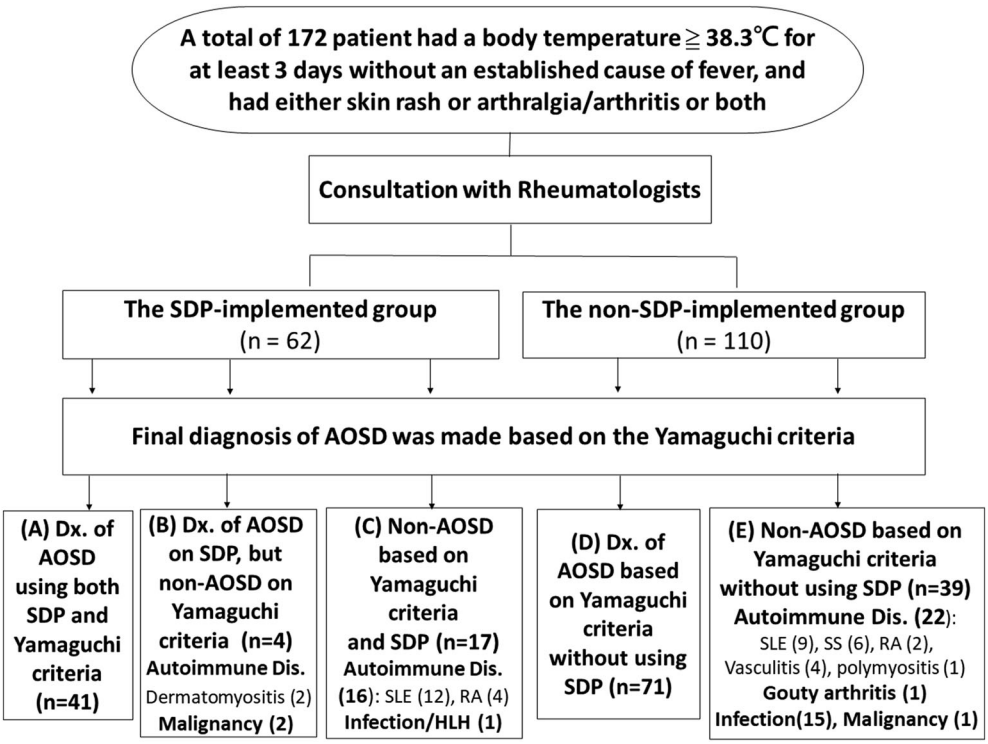

Fig. 3 Five patterns of diagnostic results depending on the combination of SDP implementation and the Yamaguchi criteria of AOSD. *SDP* streamlined diagnostic process, *AOSD* adult-onset Still's disease, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *SS* Sjögren's syndrome, *HLH* hemophagocytic lymphohistiocytosis, *Dx.* diagnosis

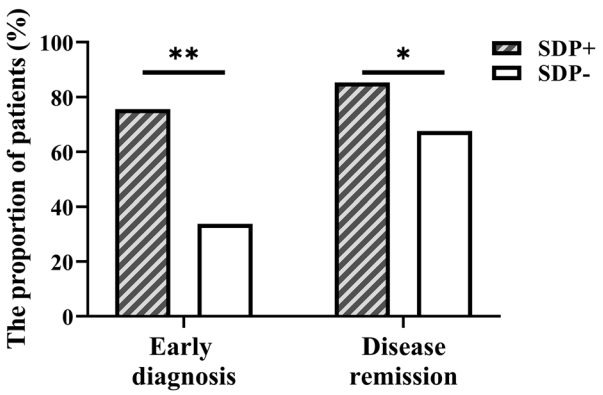

Fig. 4 Comparisons of the proportion of "early diagnosis" and the proportion of achieving disease remission after 6-month therapy between SDP-implicated and non-SDP-implicated group. $^{*}p < 0.05$, $^{**}p < 0.001$, vs. non-SDP-implicated group, as determined by chi-square test. *SDP* streamlined diagnostic process; The early diagnosis of adult-onset Still's disease (AOSD) was defined if the diagnostic lag period was 2 weeks or less than 2 weeks

febrile patients with rheumatic manifestations. The diagnosis of AOSD is made based on Yamaguchi criteria and by exclusion of infectious diseases, malignancy, or other rheumatic diseases [8]. Thus, there are clinical unmet needs to provide the SDP for expediting AOSD diagnosis based on readily available laboratory data. Accumulative evidence indicates that elevated ferritin levels, such as a fivefold increase in ferritin levels, were the diagnostic marker [12], and could be a potential discriminator for AOSD from other causes of FUO [13–15]. Given that IL-18 is the diagnostic biomarker of AOSD [19, 27], and a high IL-18 level can effectively discriminate AOSD from other autoimmune diseases [20], or infection [21, 22]. Based on these observations, we proposed the SDP, which centered on detecting hyperferritinemia, neutrophilia, and a high IL-18 level (Fig. 1), to expedite the diagnosis of AOSD.

Table 2 Logistic regression analysis of baseline variables to predict disease remission assessed at week 24 in 112 patients with adult-onset Still's disease

Baseline variables	Univariate model			Multivariate model		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age at entry, years	1.02	(0.99–1.05)	0.187			
Gender						
Male	Reference					
Female	0.68	(0.24–1.89)	0.459			
Cohort						
Non-SDP-implicated	Reference					
SPD-implicated group	2.80	(1.03–7.59)	0.044	2.36	(0.84–6.81)	0.104
Evanescent rash	2.95	(1.07–8.09)	0.036	3.80	(1.29–11.2)	0.015
Arthritis/arthralgia	0.82	(0.29–2.31)	0.709			
Sore throat	1.26	(0.53–2.95)	0.602			
Lymphadenopathy	0.65	(0.22–1.92)	0.434			
Liver dysfunction	1.13	(0.47–2.75)	0.783			
Activity score	0.91	(0.64–1.29)	0.589			
Ferritin levels	1.00	(1.00–1.00)	0.299			
ESR	0.99	(0.98–1.00)	0.097			
C-reactive protein	0.91	(0.85–0.98)	0.009	0.91	(0.84–0.98)	0.011
Leukocyte count	0.97	(0.91–1.03)	0.287			
Hemoglobin	1.42	(1.08–1.86)	0.012			
Platelet count	1.00	(1.00–1.00)	0.703			
Neutrophil %	0.96	(0.92–1.00)	0.036			
N/L ratio	0.96	(0.92–1.00)	0.056			

Variables in multivariable logistic regression: age, gender, with or without SDP, clinical features including rash, arthritis/arthralgia, sore throat, lymphadenopathy, liver dysfunction, baseline disease activity score and inflammatory parameters
OR odds ratio, *95% CI* 95% confidence interval, *SDP* streamlined diagnostic process, *ESR* Erythrocyte sedimentation rate, *N/L ratio* Neutrophil/lymphocyte ratio

In the present study, we firstly implemented the SDP to expedite AOSD diagnosis for 62 febrile patients with skin rash and/or arthritis, and the diagnosis of AOSD was finally made based on Yamaguchi criteria [8] in 41 patients. We revealed three results pairs depending on the combination of SDP implementation and the Yamaguchi criteria, and only four febrile patients were discordant. Two dermatomyositis patients with ILD manifested with hyperferritinemia and neutrophilic leukocytosis, which were the discriminative markers incorporated into the SDP in our study. The other two patients with lymphoma who manifested with cervical lymphadenopathy and hyperferritinemia had the high likelihood of AOSD diagnosis using the SDP implementation. Our results support the findings that a five-fold increase of

ferritin levels as a AOSD diagnostic marker with a specificity of 80% only [12]. The low proportion (6.5%, 4/62) of discordant diagnosis between SDP implementation and Yamaguchi criteria in our study were also like the results of a clinician-friendly algorithm proposed by Bilgin et al. [15].

In this retrospective study, we revealed a significantly less diagnosis delay and a higher rate of "early diagnosis" in the SDP-implemented group compared with the non-SDP-implemented group. Delayed diagnosis of AOSD would impede the timely institution of therapeutics and thus affect the disease remission rates. Accordingly, a significantly higher proportion of our patients in the SDP-implemented group achieved disease remission compared with the non-SDP-implemented group. The univariate logistical analysis also revealed SDP implementation as a significant predictor of achieving disease remission after a 6-month therapy. Besides, skin rash at the presentation of AOSD was a positive predictor, while high baseline CRP was a negative predictor of achieving remission. Our results resonate with a recent report that the presence of skin rash was associated with the monocyclic course of AOSD [30]. Besides, Mahdavi et al. showed that a tight-control therapeutic strategy might contribute to a high rate of disease remission [31]. Viewing that there was no significant difference in the medication use or treatment strategies between the SDP-implemented and non-SDP-implemented groups, the increased remission rates in the SDP-implemented group would be related, at least partly, to the high proportion of "early diagnosis" in those patients. Other studies also showed that a shortened diagnostic delay would allow for prompt treatment and result in a relatively benign AOSD disease course [32–34].

There are some limitations in our study. The retrospective nature of our study did not allow for obtaining all the needed information from the enrolled patients. The lack of statistical significance in the multivariate regression analysis of SDP implementation for predicting disease remission could be due to the small sample size, a limitation inherent in the study of this rare disease [31]. Besides, the selection of discriminative markers and the cutoff levels of serum ferritin and IL-18 in our SDP design should be further validated, and the beneficial effect of SDP implementation shown in our study awaits further external validation. Therefore, future long-term studies which enroll more patients and include patients with FUO of other causes as control are needed.

CONCLUSIONS

Our results show that implementing SDP could expedite the diagnostic process and improve outcomes of AOSD patients. This diagnostic process would reduce unnecessary evaluation or intervention, especially invasive procedures, or ineffective antibiotic treatment. SDP implementation may promote early diagnosis, early treatment, and disease remission in AOSD patients.

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Author Contributions. Shih-Hsin Chang conceived and designed the study, acquired the clinical data, performed the data analysis, and drafting the manuscript. Teng-Chieh Hsu acquired the clinical data and performed the data analysis. Po-Hao Huang, Chien-Chung Huang, Kai-Jieh Yeo, and Wei-Jhe Hong performed the clinical assessments on study subjects and acquired the clinical data. Po-Ku Chen performed the data analysis and statistical analysis. Yun-Hsieh Lin, Joung-Liang Lan acquired the clinical data. Der-Yuan Chen conceived and designed the study, generated the original hypothesis, acquired the clinical data,

performed the data analysis, and also revised the manuscript.

Disclosures. Shih-Hsin Chang, Teng-Chieh Hsu, Po-Hao Huang, Chien-Chung Huang, Kai-Jieh Yeo, Wei-Jhe Hong, Po-Ku Chen, Yun-Hsieh Lin, Joung-Liang Lan, and Der-Yuan Chen have no conflicts of interest to disclose.

Compliance with Ethics Guidelines. This study was approved by the institutional review board of the hospital approved this study (CMUH110-REC2-106), and the written consent was waived because this is a retrospective analysis. All procedures performed in studies involving human participants in this study were performed in accordance with the Declaration of Helsinki.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available. The original datasets used for analysis in the current study can be provided on reasonable request by contacting the corresponding author.

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